GUIDANCE[1]

ORAL EXTENDED (CONTROLLED) RELEASE DOSAGE FORMS

IN VIVO BIOEQUIVALENCE

AND *IN VITRO* DISSOLUTION TESTING

I. PURPOSE OF GUIDANCE

This guidance describes *in vivo* bioequivalence studies and *in vitro* dissolution testing recommended to applicants intending to submit Abbreviated New Drug Applications (ANDA's) for extended release products administered orally.

II. DEFINITION OF TERMS

Terms to describe formulations that do not release the active drug substance immediately following oral administration include modified/extended release (USP XXII), modified/delayed (USP XXII), controlled release, prolonged action, and sustained release. This document uses the term *extended release* to describe a formulation that does not release active drug substance immediately after oral dosing and that also allows a reduction in dosage frequency. This nomenclature accords generally with the USP definition of modified/extended release but does not specify an impact on dosing frequency. The terms *controlled release* and *extended release* are considered interchangeable in this guidance. The guidance does not consider bioequivalence studies for

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[1] This statement, prepared by the Division of Bioequivalence in the Office of Generic Drugs, is an informal communication under 21 CFR 10.90 (b) (9) that represents the best judgment of the division at this time. This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research, Food and Drug Administration, and does not bind or otherwise obligate the Center for Drug Evaluation and Research, Food and Drug Administration, to the views expressed. For further information about this guidance, contact the Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (phone: 301-594-2290; FAX: 301-594-0181).

modified/delayed release formulations. A glossary of these terms used in the guidance appears in Attachment 1.

III. REGULATORY BACKGROUND AND GENERAL REQUIREMENTS

The Drug Price Competition and Patent Term Restoration Act amendments of 1984 to the Food, Drug and Cosmetic Act gave the Food and Drug Administration statutory authority to accept and approve for marketing ANDA's for generic substitutes of pioneer products, including those approved after 1962. To gain approval, ANDA's for a generic extended release formulation must, among other things, be both pharmaceutically equivalent and bioequivalent to the pioneer extended release product, which is also termed the reference listed product as identified in FDA's *Approved Drug Products with Therapeutic Equivalence Ratings* (*The Orange Book*).

A. Pharmaceutical Equivalence

To be pharmaceutically equivalent, the generic and pioneer formulations must 1) contain the same active ingredient; 2) contain the same strength of the active ingredient in the same dosage form; 3) be intended for the same route of administration; and 4) generally be labeled for the same conditions of use. FDA does not require that the generic and reference listed extended release products contain the same excipients, or that the mechanism by which the release of the active drug substance from the formulation be the same.

B. Bioequivalence Studies

1. *In Vivo* Bioequivalence Studies for Approval

Current regulations require that bioequivalence be demonstrated between a generic extended release formulation and the reference listed product. The reference listed product is generally an extended release product subject to an approved full New Drug Application (NDA). For approval, documentation of bioequivalence must be established through performance of a series of *in vivo* bioequivalence studies that are defined in Section IV of the guidance. Approval of an ANDA will rely on data derived from evaluation of a biobatch, which is to be manufactured in accordance with the Office of Generic Drugs

Procedure and Policy Guide 22-90.

2. *In Vitro* Dissolution for Quality Control (Pre-Approval Submission of Data Required)

Quality control of the manufacture of an extended release formulation after approval may be assessed, in part, through performance of *in vitro* dissolution tests. Recommendations for the conditions under which this test may be performed are described in Section V. This section also describes how specifications for this test are developed by the applicant and approved by the Division of Bioequivalence. These data are required in the application for approval.

IV. *IN VIVO* BIOEQUIVALENCE STUDIES FOR APPROVAL

In vivo bioequivalence studies recommended for approval for extended release generic formulations are designed to document that:

- The drug product meets the extended release claim made for it.
- The drug product does not release the active drug substance at too rapid a rate (dose dump).
- Performance is equivalent between the generic and the reference listed product following single doses and dosing to steady state.
- The impact of food on the *in vivo* performance is comparable for the generic formulation relative to the innovator formulation.

The above objectives are generally met by the following three *in vivo* studies:

- A single dose, randomized, two-period, two-treatment, two-sequence crossover study under fasting conditions, comparing equal doses of the test and reference products.
- A single dose, randomized, three-treatment, three-period, six sequence, crossover, limited food effects study, comparing equal doses of the test product

administered under fasting conditions with those of the test and reference products administered immediately after a standard breakfast.

- A multiple dose, steady state, randomized, two-treatment, two-period, two-sequence crossover study under fasting conditions comparing equal doses of the test and reference formulations. For safety reasons, this study may be performed in the non-fasting state. Applicants are encouraged to submit a study protocol describing the safety considerations requiring deviation from the fasting state to the Division of Bioequivalence for review prior to execution of the study.

These studies are described in detail in Sections A, B and C below. Under certain circumstances, the Division of Bioequivalence in the Office of Generic Drugs may require additional single dose and/or multiple dose steady state studies. The following general information relative to the three *in vivo* studies is provided:

- FDA designated reference product is identified by the symbol "+" in *The Orange Book*.

- The assayed potency of the test product should not differ from that of the reference product by more than 5%.

- The clinical laboratory conducting any *in vivo* study should retain an appropriately identified reserve sample of the test and reference products for a period of five years. Each reserve sample should consist of at least 200 dosage units. For more information on retention of bioequivalence samples please refer to 21 CFR 320.63.

- A single dose two-way crossover study under fasting conditions is required for each strength of a generic extended release tablet formulation with multiple strengths. The multiple dose steady state study and the food/fasting single dose three-way crossover study are to be conducted with the highest strength only.

  For extended release capsule formulation marketed in multiple strengths, a single dose bioequivalence study under fasting conditions is required only on the highest strength, provided that the compositions of the

lower strengths are proportional to that of the highest strength, and the capsules contain identical beads or pellets. Single dose *in vivo* bioequivalence studies may be waived for the lower strengths on the basis of acceptable dissolution profiles. Multiple dose steady state and single dose food/fasting studies are to be conducted on the highest strength of the capsule formulation.

A. Single Dose Fasting Two-way Crossover Bioequivalence Study

Objective: To compare the rate and extent of absorption of a generic formulation with that of a listed reference formulation when administered in equal labeled doses.

Design: The study design is a single dose, two-treatment, two-period, two-sequence crossover with an adequate washout period (usually equal to at least 10 elimination half-lives of the drug) between the two phases of the study. Equal number of subjects should be randomly assigned to the two possible dosing sequences. The proposed protocol for the study should be approved by an institutional review board prior to initiation of the study.

Facilities: The clinical and analytical facilities used for the study should be identified along with the names, titles, and curriculum vitae of the medical and scientific/analytical directors.

Selection of Subjects: The applicant should enroll a number of subjects sufficient to ensure adequate statistical results. It is recommended that a minimum of 24 subjects be used in this study. More subjects may be required for a drug that exhibits high intra-subject variability in metrics of rate and extent of absorption. Subjects should be healthy volunteers, 18 to 50 years of age, and within 10% of ideal body weight for height and build (Metropolitan Life Insurance Company Statistical Bulletin, 1983). The selection of subjects to enter the study should be based on acceptable medical history, physical examination, and clinical laboratory tests. Subjects with any current or past medical condition which might significantly affect their response to the administered drug should be excluded from the study. Written, informed consent

must be obtained from all subjects before their acceptance into the study.

Procedure: Following an overnight fast of at least 10 hours, subjects should be administered a single dose of the test or reference product with 240 ml water. They should continue fasting for four hours after administration of the test or reference treatment.

Restrictions: Study volunteers should observe the following restrictions:

a. No alcohol or xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

b. Subjects should take no prescription medications two weeks prior to and OTC drugs one week before initiation of the study, and until after the study is completed.

c. Drinking water is not allowed from 1 hour pre-dose to 1 hour post-dose except that needed for drug dosing.

d. All meals during the study should be standardized.

Blood Sampling: In addition to the pre-dose (0 hour) sample, venous blood samples should be collected post-dose so that there are at least four sampling time points on the ascending part and six or more on the descending part of the concentration-time curve. The biological matrix (plasma, serum or whole blood) should be immediately frozen after collection and, as appropriate, centrifugation, and kept frozen until assayed.

Analysis of Blood Samples: The active ingredient should be assayed using a suitable analytical method validated with regard to specificity, accuracy, precision (both within and between days), limit of quantitation, linearity, and recovery. Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined. If the analytical method is a chromatographic method, chromatograms of unknown samples, including all associated standard curve and quality control chromatograms, should be

submitted for one fifth of subjects, chosen at random.

Pharmacokinetic Analysis of Data: Calculation of area under the plasma concentration-time curve to the last quantifiable concentration (AUC_{0-t}) and to infinity ($AUC_{0-\infty}$), C_{max}, and T_{max} should be performed according to standard techniques.

Statistical Analysis of Pharmacokinetic Data: The log transformed AUC and C_{max} data should be analyzed statistically using analysis of variance. These two parameters for the test product should be shown to be within 80-125% of the reference product using the 90% confidence interval. See also Division of Bioequivalence Guidance *Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design*.

Clinical Report and Adverse Reactions: Subject medical histories, physical examination reports, and all incidents of adverse reactions to the study formulations should be reported.

B. Multiple Dose Steady State, Two-Way Crossover Bioequivalence Study under Fasting Conditions.

Objective: To document that the steady state rate and extent of absorption of the test extended release product is similar to the rate and extent of absorption of the reference listed drug containing the same amount of the active ingredient in the same dosage formulation.

Design: The study design is a multiple dose, two-treatment, two-period, two-sequence crossover with adequate washout period between the two phases of the study. Equal number of subjects should be randomly assigned to the two possible dosing sequences. Before initiation of the study, the study protocol should be approved by an institutional review board.

Facilities: See under IV/A.

Selection of Subjects: See under IV/A.

Procedures: Extended release products which are administered once a day should be dosed following an

overnight fast of at least 10 hours; subjects should continue fasting for 4 hours post-dose. For extended release products which are dosed every 12 hours (b.i.d.), the morning dose should be given following an overnight fast of about 10 hours, and subjects should continue fasting for 4 hours post-dose; the evening dose should be administered after a fast of at least 2 hours and subjects should continue fasting for 2 hours post-dose. Each dose should be administered with 240 ml water.

Restrictions: Study volunteers should observe the following restrictions:

a. No alcohol or xanthine-containing foods or beverages should be consumed by subjects for 48 hours prior to dosing and until after the last blood sample is collected.

b. Subjects should take no prescription medications beginning two weeks prior to and OTC drugs one week before the initiation of the study until after the study is completed.

c Drinking water is not allowed from 1 hour pre-dose to 1 hour post-dose except that needed for dosing.

Blood Sampling: At least three trough concentrations (C_{min}) on three consecutive days should be determined to ascertain that the subjects are at steady state prior to measurement of rate and extent of absorption after a single dose administration in a dosing interval at steady state. The three consecutive trough samples should be collected at the same time of the day and should be comparable. For extended release drug products administered more often than every 24 hours, assessment of trough levels just prior to two consecutive doses is not recommended because a difference in the consecutive trough values may occur due to circadian rhythm irrespective of whether or not steady state has been attained. Adequate blood samples should be collected at appropriate times during a dosing interval at steady state to permit estimation of the total area under the concentration-time curve, peak concentration (C_{max}), and time to peak concentration (T_{max}).

Analytical Method: See under IV/A.

Pharmacokinetic Data: The following pharmacokinetic data are to be reported for the evaluation of bioequivalence of the generic extended release product with the reference listed product:

a. Individual and mean blood drug concentration levels

b. Individual and mean trough levels (C_{min})

c. Individual and mean peak levels (C_{max})

d. Calculation of individual and mean steady state $AUC_{interdose}$ are recommended ($AUC_{interdose}$ is AUC during a dosing interval at steady state)

e. Individual and mean percent fluctuation [= 100 * $(C_{max} - C_{min})/C_{min}$]

f. Individual and mean time to peak concentration (T_{max}).

Statistical Analysis of Pharmacokinetic Data: The log transformed AUC and C_{max} data should be analyzed statistically using analysis of variance. These two parameters for the test product should be shown to be within 80-125% of the reference product using the 90% confidence interval. Fluctuation for the test product should be evaluated for comparability with that for the reference product. For further information on statistical analysis, see the Division of Bioequivalence Guidance *Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design*.

Clinical Report and Adverse Reactions: See under IV/A.

C. Single Dose, Three-Way Crossover Food/Fasting Study.

Objective: To document that the rate and extent of absorption of the generic extended release product is equivalent to the rate and extent of absorption of the listed reference drug when both products are administered immediately after a high fat content meal [2]

[2] Each subject should consume a standardized, high fat content meal consisting of :

and to assess the effect of high fat content meal on the bioavailability of the generic extended release product.

Design: The study design is a single dose, three-treatment, three-period crossover with adequate washout period between the three phases of the study. Equal number of subjects should be randomly assigned to each of the six dosing sequences.

Selection of Subjects: A minimum of 18 subjects should be enrolled in this study. For other information on selection of subjects see under IV/A.

Procedure: Each subject should receive the following three treatments:

Treatment 1: Generic extended release product administered after a high fat content breakfast.

Treatment 2: Pioneer extended release product (reference listed drug) administered after a high fat content breakfast.

Treatment 3: Generic extended release product administered after fasting.

Following an overnight fast of at least 10 hours subjects receiving the treatment under food challenge conditions should be served a high fat content breakfast, then immediately dosed with Treatment 1 or 2 above with 240 ml water. Subjects receiving Treatment 3 should be dosed at the same time as Treatments 1 and 2 with 240 ml water only. No food should be allowed for at least 4 hours post-dose, with water allowed after the first hour. Subjects should be served standardized meals beginning at four hours during the study.

Restrictions: See under IV/A.

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one buttered English muffin
one fried egg
one slice of American cheese
one slice of Canadian bacon
one serving of hash brown potatoes
eight fluid oz. (240 mL) of whole milk
six fluid oz.(180 mL) of orange juice

Blood Sampling: See under IV/A.

Analysis of Blood Samples: See under IV/A.

Statistical Analysis: In general a comparable food effect will be assumed if the mean values of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for the generic product administered with food differ by no more than 20% from the respective mean values for the reference listed product administered with food in the study.

V. *IN VITRO* DISSOLUTION FOR QUALITY CONTROL PRE-APPROVAL

A. Dissolution Testing

Dissolution testing should be conducted on 12 individual dosage units of the test and reference products used in the bioequivalence studies. The potential for pH dependence of drug release from an extended release product is well recognized. Dissolution profiles should therefore be generated in aqueous media of the following pH ranges: 1 - 1.5, 4 - 4.5, 6 - 6.5, and 7 - 7.5. Early sampling times of 1, 2, and 4 hours should be included in the sampling schedule to provide assurance against premature release of the drug (dose dumping) from the formulation. The general dissolution conditions to be followed are shown below:

1.	Apparatus	USP XXII Apparatus 1 (rotating basket) for capsules USP XXII Apparatus 2 (paddle) for tablets
2.	Rotation Speed	100 rpm (basket) 50 and 75 rpm (paddle)
3.	Temperature	37 $\pm$ 0.5°C
4.	Units To Be Tested	12
5.	Dissolution Medium	900 ml of aqueous media of various pH
6.	Sampling Schedule	1, 2, 4 hours, and every two hours thereafter,

		until 80% of the drug is released.
7.	Tolerances	As established.
8.	Content Uniformity	Content uniformity testing of the test product lot should be performed as described in the USP XXII.

B. Specifications

Specifications for the dissolution procedure to assure quality control will be determined on a case by case basis (usp case 3). In general further validation will be required to expand dissolution specifications beyond those established for the biobatch.

VI. BIBLIOGRAPHY

1. Skelly JP, Amidon GL, Barr WH, et al. Workshop Report: *In vitro* and *in vivo* testing and correlation for oral controlled/modified-release dosage forms. *Pharmaceutical Research* 1990;7:975-82.

2. Dighe SV, Adams WP. Bioavailability and bioequivalence of oral controlled release products: A regulatory perspective. In: Welling PG, Tse FLS, eds. Pharmacokinetics: Regulatory, Industrial, and Academic Perspectives. New York: Marcel Dekker Inc., 1988:307-36.

3. Skelly JP, Barr WH. Regulatory assessment. In: Robinson JR, Lee VHL, eds. Controlled Drug Delivery--Fundamentals and Applications. 2nd edition. New York: Marcel Dekker Inc., 1987:294-334.

4. Chien YW. Regulatory considerations in controlled drug delivery. In: Chien YW ed. Novel Drug Delivery Systems. Second edition, New York: Marcel Dekker Inc., 1992:747-76.

ATTACHMENT 1

Glossary

Delayed release dosage form :

A delayed release dosage form is one that releases a drug(or drugs) at a time other than promptly after administration.

Extended release dosage form:

An extended release dosage form is one that allows at least a twofold reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g. as a solution or prompt drug-releasing, conventional solid dosage form).

Modified release dosage form:

A modified release dosage form is one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms. Delayed release and extended release dosage forms are two types of modified release dosage forms.

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